論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Ｎａｍｅ	WANG YAN
論文題名 Title	PI3K/mTOR dual inhibitor GSK458 and arsenic trioxide exert synergistic anti-tumor effects against ovarian clear cell carcinoma （卵巣明細胞癌にはPI3K/mTOR 阻害剤 GSK458 と三酸化ヒ素の併用が相乗的な抗腫瘍効果を示す）

論文内容の要旨

〔目的(Objective)〕

Ovarian clear cell carcinoma (OCCC), particularly advanced or recurrent settings, is generally resistant to platinum-based chemotherapy, warranting novel therapeutic strategies. Mutations in the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin kinase (PI3K/AKT/mTOR) pathway are frequently reported in OCCC. Therefore, we hypothesized that the PI3K/mTOR dual inhibitor, GSK458, and arsenic trioxide may exert synergistic anti-tumor effects on OCCC.

〔方法(Methods)〕

We investigated the effects of GSK458, As2O3, and their combination (GSK458–As2O3) on cell viability, colony formation, and apoptosis in seven OCCC cells. Mechanistically, transcriptomic differences were assessed among the groups. Additionally, their anti-tumor effects were evaluated on the three-dimensional cultures of OCCC patient-derived xenografts (PDXs) as well as in vivo.

〔成績(Results)〕

Low-dose GSK458–As2O3 exerted synergistic anti-tumor effects in vitro. Viability of the three-dimensional OCCC PDX cultures treated with GSK458–As2O3 decreased to 23.8% of that of the control. RNA sequencing revealed that the mechanism was associated with cell cycle and DNA damage repair. GSK458–As2O3 synergistically inhibited the PI3K/AKT/mTOR pathway and angiogenesis and increased apoptosis. Compared to any monotherapy, the combination treatment significantly suppressed tumor growth in vivo, thereby enhancing survival.

〔総括(Conclusion)〕

Overall, our findings highlight the potential of the novel GSK458–As2O3 combination for OCCC treatment.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

Ovarian clear cell carcinoma (OCCC), particularly advanced or recurrent settings, is generally resistant to platinum-based chemotherapy, warranting novel therapeutic strategies. Mutations in the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin kinase (PI3K/AKT/mTOR) pathway are frequently reported in OCCC. Therefore, we hypothesized that the PI3K/mTOR dual inhibitor, GSK458, and arsenic trioxide may exert synergistic anti-tumor effects on OCCC. We investigated the effects of GSK458, arsenic trioxide, and the combination of GSK458 and arsenic trioxide on cell viability, colony formation, and apoptosis in seven OCCC cells. Mechanistically, transcriptomic differences were assessed among the groups. Additionally, their anti-tumor effects were evaluated on the three-dimensional cultures of OCCC patient-derived xenografts as well as in vivo. Low-dose combination of GSK458 and arsenic trioxide exerted synergistic anti-tumor effects in vitro. Viability of the three-dimensional OCCC patient-derived xenograft cultures treated with the combination of GSK458 and arsenic trioxide decreased to 23.8% of that of the control. RNA sequencing revealed that the mechanism was associated with cell cycle and DNA damage repair. The combination of GSK458 and arsenic trioxide synergistically inhibited the PI3K/AKT/mTOR pathway and angiogenesis and increased apoptosis. Compared to any monotherapy, the combination treatment significantly suppressed tumor growth in vivo, thereby enhancing survival. Overall, our findings highlight the potential of the novel combination of GSK458 and arsenic trioxide combination for OCCC treatment.To the best of our knowledge, this study is the first to reveal that GSK458 synergistically enhanced the anti-tumor effects of As2O3 against OCCC in vitro and in vivo via downregulation of the PI3K/AKT/mTOR pathway in OCCC cells. Therefore, GSK458–As2O3 combination can be used to enhance the drug efficacy and decrease the toxicity in OCCC treatment. Furthermore, our findings highlight the potential clinical applications of GSK458–As2O3.

This research is worth being granted a doctoral degree(medicine).